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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,882	NOLAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003 and 06 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is a reply to the Amendment and Response of 3 November 2003 and Supplemental Amendment of 6 January 2004 filed in response to the Non-Final Office Action mailed 22 October 2003. Claims 21 and 24-26 were considered in the 22 October Office Action. Claims 21 and 26 were amended in the 6 January Paper. Claims 21 and 24-26 are pending and under consideration.

Response to Amendment

Priority

Applicant has amended the first line of the specification to claim benefit of the earlier filed US Applications 09/453,610 and 60/110,951. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 199(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

There is no support for a broad negative limitation which excludes plant cells from the scope of the eukaryotic cells used in the method (*i.e.*, "the cell is not a plant cell") as recited in the instant claims 21 and 26 in any of the applications named in the first line of the specification.

Although the priority documents contemplate various cell types that are not plant cells, the specification of the 09/453,610 explicitly states "[c]ells contemplated as recipients or 'hosts' for the chromosomal DNA include...essentially any cell that can be exploited *ex vivo* for the purposes of gene delivery" (page 8, paragraph 4). Thus, the broad exclusion of plant cells from the cells contemplated as recipients constitutes new matter. Therefore, the claims are not entitled to benefit of any of the prior applications.

Furthermore, there is no reference to "a liposome" in the 09/453,610 application, which is the only parent application that was copending with the instant application. The 09/453,610 application contemplates only an "encapsulated single chromosome" with no specific reference to the encapsulating substance (see especially the second full paragraph on page 12 and the originally filed claim 21). Although the 09/453,610 application claims benefit of 60/110,951, which does contemplate a liposome encapsulated chromosome, there is no incorporation by reference of the subject matter of 60/110,951 into the 09/453,610 disclosure. A priority claim under 35 U.S.C. 119(e) does not amount to an incorporation by reference of the application(s) to which priority is claimed (M.P.E.P. 201.06(c)). Therefore, there is no support for claims limited to encapsulation of a chromosome into a liposome in the application immediately preceding the instant application in the continuity chain.

Applicant has also amended the specification to claim benefit of US Provisional application 60/110,950. However, the instant application is not entitled to benefit of the 60/110,950 application because the applications were not copending.

Specification

The amendment filed 6 January 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Applicant has amended the specification to incorporate the contents of prior applications 09/453,610; 60/110,950; and 60/110,951. There was no statement incorporating these applications by reference in the originally filed disclosure. Although the present application claims benefit of the prior applications, a priority claim under 35 U.S.C. 120 or 119(e) does not amount to an incorporation by reference of the application(s) to which priority is claimed (*Id.*) Therefore, the subject matter incorporated by reference to the prior applications that was not present in the instant application at the time of filing constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

Claims 21 and 24-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/34436 (hereinafter, '436).

Although Applicant has sought to overcome the rejection by perfecting the priority claim, the instant claims are not entitled to benefit of the previously filed applications because none of the applications contemplates the method wherein the host cell is limited to not being a plant cell.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Neither the originally filed declaration nor the substitute declaration filed 10 October 2000 make reference to the preliminary amendment filed with the instant application. Therefore, the preliminary amendment is not considered part of the original disclosure (see MPEP 608.04(b) and 714.01(e)). There is no support for the broad negative limitation "said cell is not a plant cell", which is added in the preliminary amendment, in the originally filed disclosure. Although the disclosure contemplates various cell types that are not plant cells, the specification explicitly states "[c]ells contemplated as recipients or 'hosts' for the chromosomal DNA include...essentially any cell that can be exploited *ex vivo* for the purposes of gene delivery" (paragraph [0025]). Thus, exclusion of plant cells from the cells contemplated as recipients constitutes new matter. This rejection can be overcome by filing a substitute declaration which refers to the preliminary amendment.

Claims 21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in vitro* introduction of at least one chromosome into a eukaryotic cell, does not reasonably provide enablement for the method wherein the cells into which the chromosomes are introduced are implanted as part of an *ex vivo* gene therapy protocol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method for *ex vivo* introduction of at least one chromosome into a eukaryotic cell. In paragraph 3, the specification states, "[t]he introduction of intact single chromosomes (i.e., large protein/DNA complexes) into cells offers unprecedented usefulness as a gene therapy tool..." As the specification contemplates utilizing the method as a gene therapy tool, and there is nothing in the claim that excludes reintroducing the modified cells into an animal, the claims reasonably encompass a method of *ex vivo* gene therapy.

State of the prior art and level of predictability in the art: At the time of filing, *ex vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today".

Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published at approximately the same time as the effective filing date of the instant claims, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future"**, beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claims of the instant application are not limited to treatment of any particular condition and thus encompass methods of treating any conditions that might be amenable to gene therapy. However, Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660).

Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *ex vivo* by expressing a therapeutic gene was extremely low.

Amount of direction provided by the inventor and existence of working examples: specification is silent with regard to how the skilled artisan might overcome the myriad of obstacles facing one seeking to practice a method of *ex vivo* gene therapy. Although the specification provides speculation that delivering genes on chromosomes might be better than other delivery methods, the instant application is devoid of working examples. Furthermore, the teachings of the specification provide no guidance with regard to effective therapeutic genes, dosage and routes of administration. As none of these aspects of *ex vivo* gene therapy were conventional in the art at the time of filing, neither the art nor the instant specification provide the skilled artisan with guidance that would enable any method of *ex vivo* gene therapy according to the instant claims.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods

of the instant claims for *ex vivo* gene therapy without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression and the absence of existing working examples, the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to make the full scope of the invention without undue experimentation.

Claims 21 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "substantially simultaneously". The phrase has no conventional meaning and the specification provides no definition of the phrase "substantially simultaneous". It would seem that the electric pulse need not be applied at the same time as the chromosome, but only that the application be within a range of non-simultaneous intervals which are "substantial" according to some undefined measure. Applicant should clarify how "substantially simultaneous" is to be distinguished from "unsubstantially simultaneous" and indicate where the specification teaches the skilled artisan how to make such a distinction.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

DAVID GUZO
PRIMARY EXAMINER